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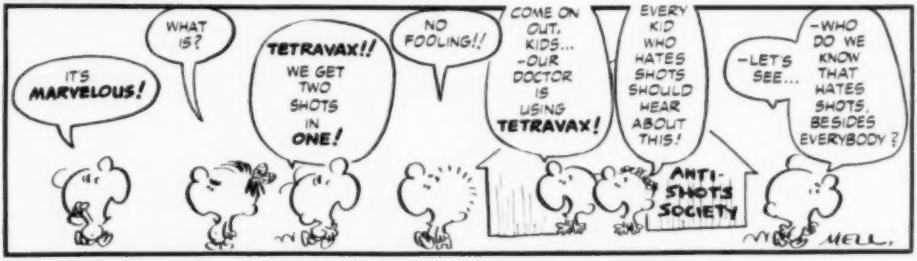
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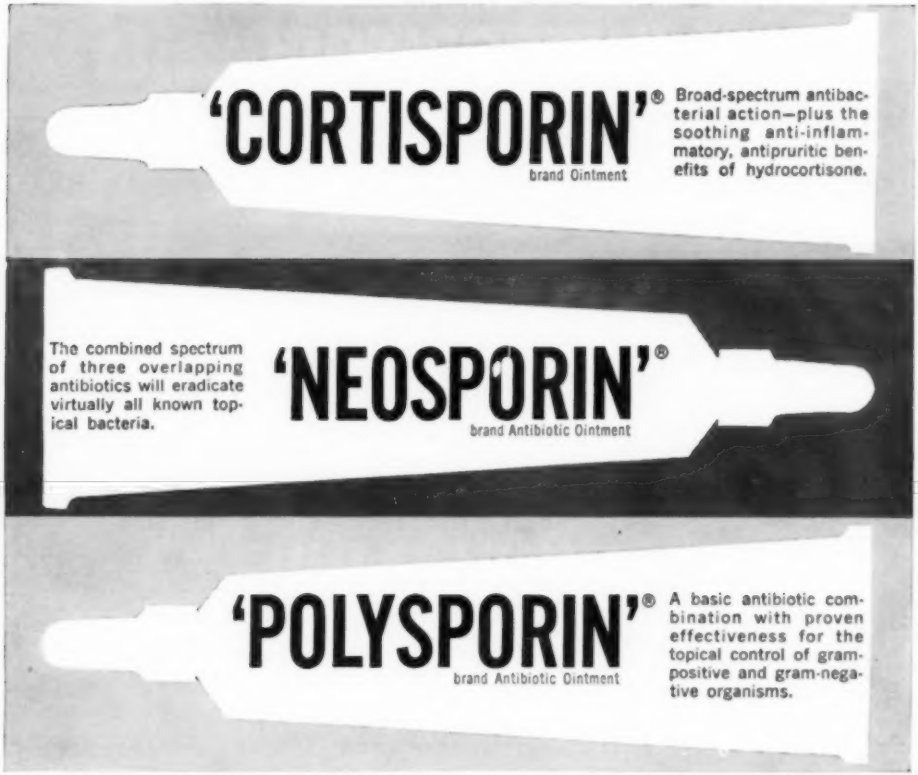
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April 1961

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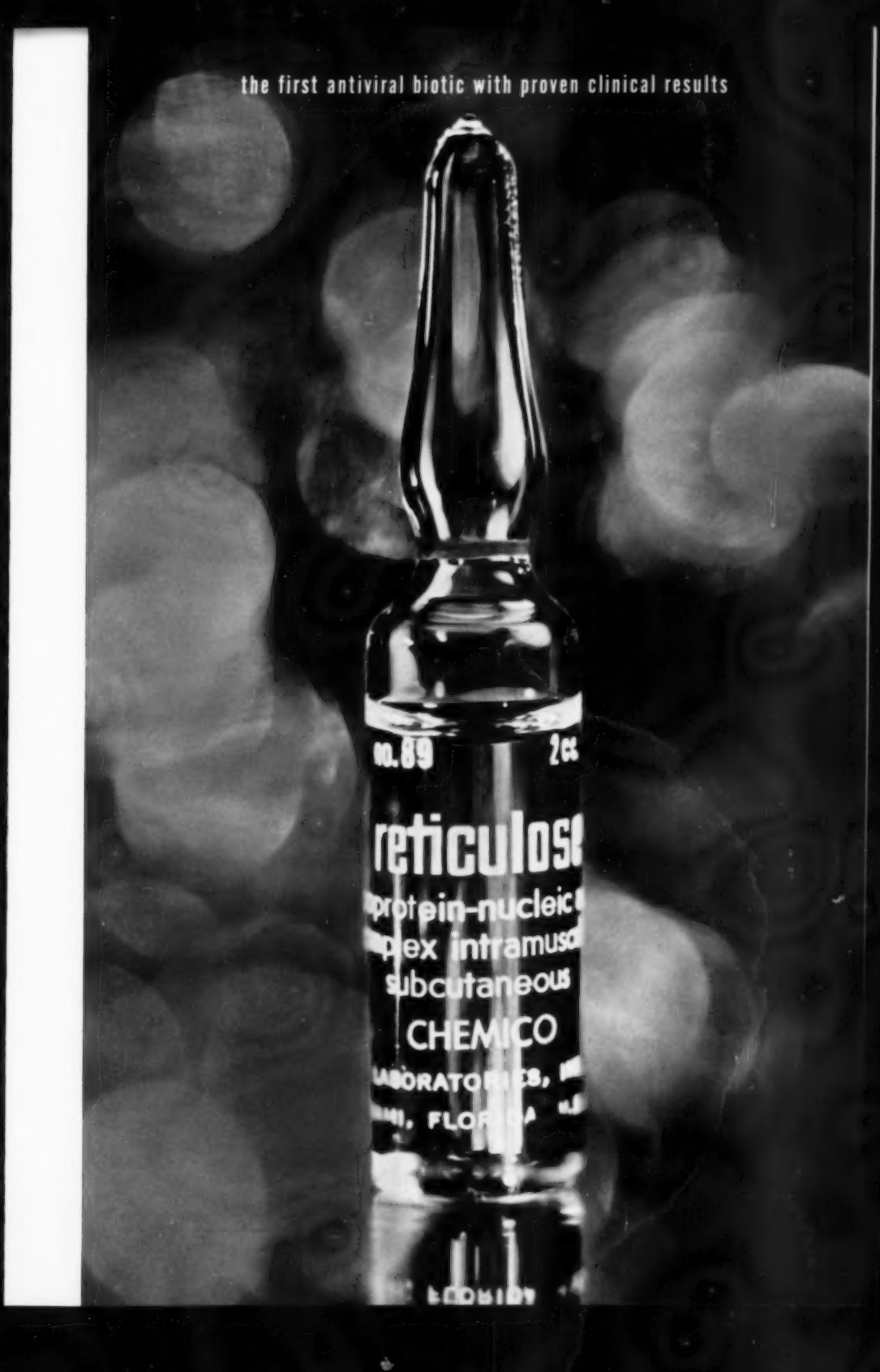
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*T.M.

Clinical Evaluation of Brain Damage In Cases of Cerebral Palsy*†‡

Cyril B. Courville, M.D.
California

In a meeting of this Society in Providence, Rhode Island, in October, 1958, some clinical investigator made the statement that it is possible to predicate the nature of brain damage in cases of cerebral palsy on the basis of the clinical syndrome presented. Whether or not such an accomplishment would advance our knowledge with respect to an understanding of the cause or would improve the management of any given case, such a possibility would give one a great deal of personal satisfaction. I have not been intimately connected with the problem of clinical evaluation of any large number of patients, being more concerned with the pathology of cerebral palsy. However, I have had the opportunity of comparing the clinical records with the findings at autopsy in 160 verified cases. This has furnished an opportunity to determine the possibility of a correct lesion diagnosis on the basis of the nature and distribution of the motor difficulty.

On this basis I was more impressed with errors in diagnosis than with the accuracy of the clinicians concerned, who were often content to consider the problem as one of "birth injury" rather than to attempt to denote either the location or the nature of the brain disease.

This study is therefore directed to an investigation of this group of records. As it turned out, this report seems to be more of a rebuttal of cited conclusions implying the accuracy of clinical diagnosis. If my deductions are not correct, it must be assumed that some clinicians who deal with the problem of cerebral palsy are much better than most others when it comes to detection of the

*From the Cajal Laboratory of Neuropathology, Los Angeles County Hospital, and the Division of Nervous Diseases (Neurology), College of Medical Evangelists, Los Angeles, California.

†This study was made possible by a grant (B-1248) from the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

‡Read before the annual meeting of the American Academy for Cerebral Palsy, Pittsburgh, Pa., on October 7, 1960.

precise etiologic agent involved as well as location of the damage which that agent has been able to produce in the brain of a given patient.

To attack the problem in a reasonably systematic way, I shall investigate the following aspects of the problem: (1) The pathological lesions on which the clinical picture and the course of the disorder can be based, viewed from (a) the onset and course of the palsied state, as well as (b) the location and nature of the resultant lesion; and (2) The general problem of clinical diagnosis with an analysis of the case records at hand to note the several lesions which can produce a given clinical syndrome.

THE PATHOLOGICAL LESIONS ON WHICH THE CLINICAL PICTURE AND COURSE OF THE DISORDER CAN BE BASED, NOTING FIRST THE ONSET AND COURSE OF THE PALSIED STATE

As in any neurological disease, the clinical diagnosis is usually based upon (1) the clinical course of the disorder and (2) the nature of the disease process. This will explain why it is necessary to consider both these factors in attempting to make a lesion diagnosis in a given case of cerebral palsy. On the basis of the *clinical course of the disorder* leading to the palsied state, there is usually one of several possibilities: (1) The onset of symptoms within a few days after birth with persistence thereafter, associated with either (a) a progressive downhill course to death after weeks or months, or (b) a longer survival period without material progression over a period of years, death being due to some intercurrent situation.

The onset of cerebral palsy some time after an apparently normal birth may occur either as (2) an acute episode with an obvious cause which suggests *per se* the nature of the process involving the brain or (3) a slow onset with symptoms becoming apparent only as the infant develops. In the first situation the course may still be progressive to fatal issue or may actually improve to a certain level over the months or years. In the second case the development is usually gradual until the fullblown palsied state is reached, one which is often complicated by intellectual impairment and/or convulsive or other types of seizures.

The second factor, namely the *nature of the disease process*, can give us relatively little help in this case because in all instances we have a gross motor disability as implied in the very term "cerebral palsy." The associated disabilities of intellectual impairment and

convulsive disorder assist one but little because of the frequency with which such symptoms are to be found in this group of cases. It is nevertheless fundamental to the present thesis to consider the grouping of the motor disorders which will constitute the very basis of the clinical evaluation to be considered later on. They are grouped as (1) monoplegias, (2) hemiplegias, (3) double hemiplegias, (4) paraplegias, (5) quadriplegias with decorticate rigidity, and (6) choreo-athetosis. A final grouping often considered in connection with cerebral palsy, (7) the ataxic-atonic group, will not be dealt with in this study because in a strict sense these cases, at least in their pure state, are not motor disorders. Also, their consideration introduces the entire problem of the multitude of cerebellar diseases, which would take us too far afield. More will be said about the true akinetic and dyskinetic disorders subsequently.

A SURVEY OF THE PATHOLOGICAL LESIONS ON WHICH THE CLINICAL PICTURE AND COURSE OF THE PALSIED DISORDER CAN BE BASED AS EVALUATED BY THE LOCATION AND NATURE OF THE LESIONS THEMSELVES

My experience in dealing with resultant lesions apparently responsible for the cerebral palsied states has led me to formulate certain principles in their evaluation. In this connection we shall consider (1) the congenital malformations, (2) the nature of brain lesions consequent to well-defined clinical causes, (3) the nature of brain lesions resulting from the poorly defined causes, noting in particular paranatal anoxia, (4) the wide divergence in the degree of physical change in the tissues of the brain capable of producing motor symptoms and signs, (5) the variety of gross lesions which seem to be capable of producing similar clinical states, (6) the frequency with which the brain of a cerebral palsied child may show a combination of two or more types of lesions (lesion-complexes), and (7) the tendency for the brain to show these multiple lesions in different parts of the motor systems which would therefore modify the clinical picture. These factors will now be considered independently.

The Problem of Congenital Malformations. The presence of a congenital malformation in the brain presents a genuine problem in diagnosis. This is because in the clinical history there is no distinct episode marking the onset of the disorder which would suggest the nature of the cerebral lesion. The clinical picture is often atypical, making any attempt to base a specific diagnosis as to the nature of

the lesion extremely difficult if not impossible. For example, the disclosure on a pneumoencephalogram or at autopsy of a widespread cortical dysmorphogenesis, the absence of the corpus callosum, the presence of a gross cerebral defect, or agenesis of the cerebellum often comes as a complete surprise. How is the clinician to arrive at a precise diagnosis under such circumstances?

Value of Known Etiology in Diagnosis. The brain lesions consequent to known well-defined causes usually follow a recognized pattern. Thus, if the etiology of a given cause of cerebral palsy is clearly established, in the majority of cases the nature of the cerebral lesions, both gross and microscopic, may be anticipated. This applies to such factors as mechanical injury to the brain at birth (which may be associated with chronic subdural hematoma), kernicterus (with its cortical and ganglionic symptomatology), scarlet fever (with its tendency to produce arterial thrombosis), otitis media and mastoiditis (with venous thrombosis as a common sequel), postinfectious encephalitis (with diffuse perivascular demyelination), etc. In all these situations, the type of lesion produced in the brain may be presumed within a narrow margin of error.

Paranatal Anoxia Responsible for a Variety of Lesions. The greatest exception to the rule noted in the preceding paragraph is found in examples of paranatal anoxia. In the first place, the occurrence of anoxia at the time of birth is often not recognized at all or is confused with the mechanical type of birth injury with hemorrhage as its chief complication.* More than this, anoxia is capable of producing such a variety of changes that even though it seems clear that this is the cause of the cerebral lesions responsible for cerebral palsy, it is by no means certain what lesions may be present (Courville, 1952). And because paranatal anoxia is probably

*I cannot forebear answering the assumptions as to the cause of brain damage in early life as set forth by so able a student of the problem as Malamud (1959). This investigator endeavors to prognosticate the nature of brain damage on the basis of the apparent etiology of the lesion in "birth injury" on one hand and "postnatal illness" on the other. He has divided the cerebral lesions in his series of 162 cases of cerebral palsy verified at autopsy (almost identical in number with that of Courville) into two groups. In Group A he included "subcortical lesions" (nodular or sclerotic atrophy of the cerebral cortex, status marmoratus of the corpus striatum and thalamus, and cystic degeneration of the cerebral white matter). Malamud concludes that the lesions in this group (101 cases—62 per cent of the series) were due to "birth injury" (in 86 per cent of the cases a history of birth injury was elicited). In Group B the lesions in 36 cases (22 per cent of the series) were those affecting the cerebral convolutions (lobar, hemispheral or generalized) and were the result of postnatal illness (such as infections) in 90 per cent of these cases. In 25 other cases (16 per cent of the series) in which *both* cortical and subcortical lesions were found there was a history of normal birth and postnatal history in 14 and a history of both "birth injury" and postnatal illness in 10. In only 12 cases was the history of the cause of the disability unknown.

As Dr. W. G. Anderson pointed out in his discussion of the papers of Dr. Malamud and myself (which were delivered in the same symposium), the unfortunate feature of any discussion of etiology in cases of cerebral palsy is the lack of preciseness in the use of the term of "birth injury." This was evident in the remarks of Dr. Malamud

the greatest single factor in the production of brain damage in early life, the nature of the cerebral lesions is particularly apt to be misinterpreted from a clinical viewpoint.

Variations in the Degree of Physical Alterations in the Brain. In patients with brain damage of uncertain cause, experience has shown that there is a remarkable variation in the degree of change capable of producing motor disability. For example, in a typical case of hemiplegia or paraplegia, one may be surprised to find that the brain appears to be remarkably normal on a pneumoencephalogram or at autopsy. The brain may indeed be somewhat smaller than average for a person of this age, and may weigh less than it should for a person of a given size and development. Nevertheless, the individual convolutions are all the same size and are uniform in their conformation. Microscopic study of the population of nerve cells shows that it is the loss of these cells in the motor cortex that is the responsible factor for the paralytic phenomena in this case. On the other hand, the brain may show rather severe gross lesions (effects of pressure of a subdural hematoma, gross softening, nodular atrophy, cyst formation, etc.) so that no question as to the cause of the motor deficit could possibly exist.

Several Cerebral Lesions Capable of Producing Motor Symptoms. Perhaps the most important difficulty in the evaluation of the possible cause of motor symptoms and signs lies in the fact that any one of several lesions may be the specific cause of the disability. This is particularly true of the variety of change consequent to paranatal anoxia. For example, any type of lesion found in the central region, including softening, nodular atrophy, porencephaly, cortical or subcortical cyst formation, or even structural alterations in the underlying basal ganglia can produce spastic paralysis of the contralateral extremities. In a given case, how then is the clinician to know the specific type of lesion present?

(page 149 of his article) when he included such conditions as placenta praevia, prolapse of the cord, and cord around the neck in the term "birth injury." At the same time, the significance of such objective signs of cerebral anoxia as "apnea and cyanosis . . . requiring resuscitation" is ignored. Moreover, Doctor Malamud has much more faith in the clinical records of the State Hospitals obtained second or third hand than I have in my own records often obtained at first hand from the obstetrician and/or the parents as far as the details surrounding the birth of the child are concerned.

Doctor Malamud's profound belief in Schwartz' theory of the mechanism of "birth injury," propounded some 40 years ago and recently reviewed by him (1956), in my opinion does not constitute proof of its reliability. In the past three years I have taken occasion to review this concept of brain damage which is based on occlusion of the internal system of Galen incident to development of certain intrauterine stresses during delivery. I first reviewed the nature of cerebral lesions incident to instances of verified cases of venous thrombosis of the cerebral channels in early life from other causes (Courville, 1958, 1959b). The arguments of some other and probably circulatory cause for these lesions were then explored (Courville, 1959 a and c) and some evidence offered in favor of an anoxic etiology presented. Other studies on the causes of specific softening of the cerebral white matter have now been completed and will soon be submitted for publication (Young and Courville). In conclusion it may be said that the theory proposed by Schwartz and so warmly espoused by Malamud, as an explanation of the cerebral lesions causing cerebral palsy, deserves the most careful study by those concerned with this subject, the references cited being readily available to all readers.

Problem of Multiplicity of Lesions Affecting the Motor Pathway. As though the above mentioned problem in estimation of the nature of brain damage were not enough, one faces the possibility that two or even more lesions may affect the motor cortex and pyramidal systems as well as the subsidiary systems of the extrapyramidal system with its own cortex, underlying corpus striatum, accessory nuclei in the upper brain stem and connecting pathways. Even the cerebellum may be damaged to a degree to modify the end picture as has been recently shown (Courville, 1959 c). Therefore, if one is astute enough to suspect that the degree of spasticity present in a given case is the result of a lesion of the corpus striatum, how can he know whether or not some other lesion of the motor cortex is not also present? This is doubly true, since the intricacies of function of the entire extrapyramidal system, particularly that portion of it involved in the corpus striatum and its intrinsic connections is still not clearly established. On this basis, one can only wonder at the optimism of some clinical workers in the field of cerebral palsy who seem to have no difficulty in assessing in full the nature and extent of brain damage!

Multiplicity of Brain Lesions as a Difficulty in Lesion Evaluation. A final note of pessimism in the matter of clinical diagnosis must be added. Not only is it a fact that more than one lesion may produce a given motor effect, and that more than a single lesion may be present in the motor (pyramidal, extrapyramidal, and cerebellar systems) pathway, but in addition, there may be lesions elsewhere in the brain which may modify one's clinical impressions of the nature and degree of motor disability. At least two aspects of this part of the problem should be mentioned. The influence of epileptogenic lesions with the element of irritability of the motor cortex as well as the possibility of petit mal activity, occurring even in form of *status epilepticus*, and finally the occurrence of psychomotor or sensory attacks are all certainly capable of modifying motor functions. But even more important, the factor of intellectual impairment with an associated lack of volition may raise the question of whether the child *cannot* perform certain motor functions, or whether he *wills* not to do so. In case of widespread alterations of the cerebral cortex or subcortex, or the presence of multiple lesions affecting various parts of the cerebral hemispheres, these disturbances in physiology sometimes play a significant part in any study of the motor functions. This would be further complicated if there intruded the problem of auditory speech difficulty in which the child could not understand instructions from the examining physician.

A COMPARISON OF CAUSATIVE LESIONS WITH RESULTANT MOTOR SYNDROME

On the basis of pathological observations made in a large series of cases of cerebral palsy verified at autopsy, it is now appropriate to make a comparison between the causative lesion or lesions and the resultant motor syndrome present. Only a fraction of the total series of 160 cases could be used because of lack of accuracy or completeness of the clinical history.* Yet there were sufficient examples of monoplegia, hemiplegia, double hemiplegia, quadriplegia with or without decortical rigidity, paraplegia, and choreoathetosis to compare with the lesions which apparently caused them. It is this smaller group of cases which have become available for this part of the study. The lesion-diagnosis verified by examination of the brain itself will be collated with the type of motor disability in the following section.

Monoplegia. As was to be expected, there were relatively few cases with monoplegia in this autopsy series. Since such a limited degree of motor disability without any other major symtomatology does not carry with it any degree of lethality, those cases with either a monoplegia of the faciobrachial type or of a single lower extremity would be only chance observations. In fact, one of these was a woman who at birth had some sort of acute episode presumed to be anoxic in character. She lived to the ripe old age of 80, to die of some intercurrent difficulty (Courville, 1953). There were five cases in all in this group. In two cases, the cause of the monoplegia was a lobar sclerosis involving part of the central convolution. In one case a cerebral hemiatrophy with a focal postcentral scar (microgyria) was found. In still another the child had developed an obstructive internal hydrocephalus associated with generalized cerebral atrophy as a complication of meningitis (the reason for the monoplegia was not apparent grossly). In the fifth case (cited above) an atrophy of the lower frontal and parietal convolutions bordered with microgyria was disclosed. It is suggested by this very small series that focal microgyria or a focal cortical scar would

*In preparing the dossiers to accompany the autopsy record, every effort was made to determine the complete and correct clinical story in each case. This was not too difficult in cases in which the child had been observed during life in a large hospital or clinic. Nevertheless, an exact picture of possible etiology was often lacking, even when the parents could be questioned. There seemed to be a "conspiracy of silence" about any possible accident at birth in many instances, and only imperfect glimpses of disaster can be obtained. Even more amazing is the lack of a precise description of the motor difficulty, the most important single feature in these cases. This survey of records has made apparent the need to review again every reference to the extent, nature, and degree of paralysis implied in many of these cases. When this re-survey has been completed, a larger percentage of cases will be available for a similar evaluation. However, a sufficient number of examples were found to make this preliminary report worthwhile.

be the most likely cause of a monoplegia, but the clinical state could be caused by any type of focal lesion, affecting only a part of the motor cortex.

Hemiplegia. There were seven cases in which hemiplegia was present as the chief motor symptom. In one case, the brain appeared to be "normal" grossly. In another case, a porencephalic defect in the central region was the obvious cause. In a third case, cerebral hemiatrophy was the only change noted in the brain. In the other four cases, the motor strip of one hemisphere was involved in nodular cortical atrophy (central lobar sclerosis) although other portions of both hemispheres were also affected in some instances. This type of cortical change could therefore be presumed to be the most common cause of hemiplegia, one which might well be associated

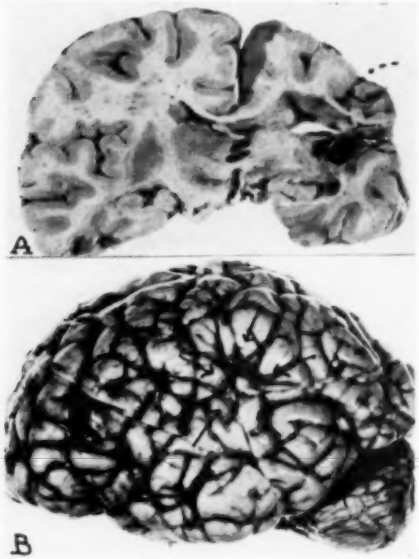

Fig. 1. Cerebral lesions causing monoplegia. A. Marked cortical-subcortical atrophy in an 80-year-old woman with faciobrachial monoplegia dating back to birth. B. Focal cortical scar, presumably vascular, causing paralysis of right arm.

with a porencephalic defect, as is not infrequently the case (Courville, 1960 c).

Double Hemiplegia. It was difficult to distinguish double hemiplegia (bilateral cortical disease) from true quadriplegia (gross degeneration of brain tissue including primary or secondary damage to the brain stem), but as nearly as could be learned from the often meager clinical data, there were 11 fairly clear-cut cases and

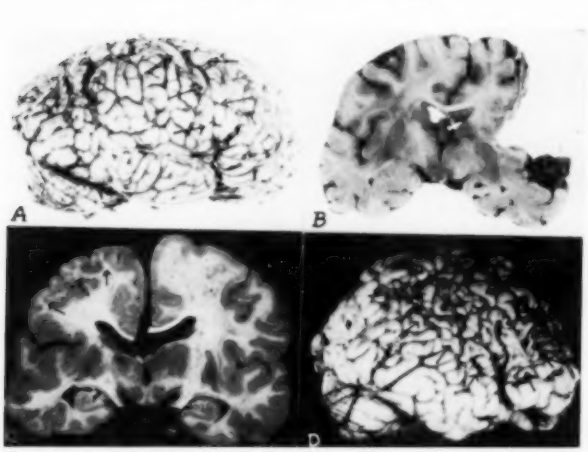

Fig. 2. Cerebral lesions causing hemiplegia. A. Incomplete cleft in region of right motor cortex resulting in left hemiplegia. B. Gross porencephalic defect. Note atypical morphogenesis of left motor cortex. C. Right cerebral hemiatrophy with abnormal development of motor cortex. D. Lobar sclerosis (ulegyria) in right pre- and postcentral area resulting in left hemiplegia.

another one which was somewhat questionable. In one case, a grossly normal brain was found at autopsy. In another, a widespread congenital dysmorphogenesis (congenital microgyria) was found. In one instance, true mechanical trauma with cortical compression by subdural hematoma seemed to be the cause. In another case, a porencephalic cavity on one side and nodular cortical atrophy on the other were noted. In three cases a generalized cerebral cortical atrophy was present, with an appreciable greater degree on one side in one of them. In three other cases and in the one questionable case, bilateral central nodular atrophy was found, either in symmetrical or asymmetrical distribution (in one of these, basal ganglion disease was also present). In one case a post-meningitic hydrocephalus, with unequal degrees of dilatation of the lateral ventricles was present as the only accountable lesion. In still another case, status dysmyelinisatus with dystonia was the only significant lesion found.

Quadriplegia without Decortical Rigidity. Quadriplegia without noticeable decortical rigidity was noted in two cases, one with generalized cortical atrophy, the other with an acquired hydrocephalus.

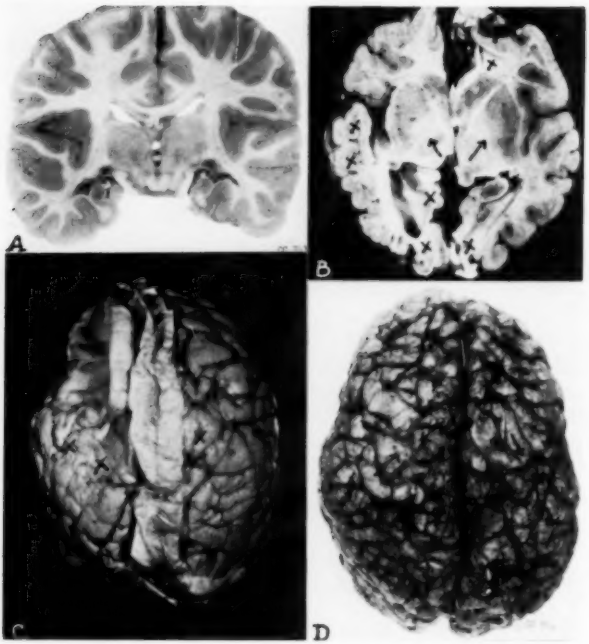

Fig. 3. Cerebral changes in cases of double hemiplegia. A. "Normal" brain in patient with double hemiplegia. B. Cortical-subcortical alterations with variable localization in the two hemispheres. Extremely small brain of a 3½-year-old paralytic, epileptic and mentally deficient girl asphyxiated at birth. C. Gross frontal lesion on left with circumscribed cortical changes in right central area resulting from severe craniocerebral injury during infancy. D. Incomplete cleft right motor area associated with atypical development of left motor cortex.

Quadriplegia with Decortical Rigidity. This fairly typical syndrome of spasticity in all extremities associated with opisthotonus was found in a group of cerebral palsied children in the first three years of life, presenting a downhill course to death. It was found in gross severe lesions of the cerebral hemispheres. In four cases there was subtotal softening of the cerebral hemispheres (Courville, 1960 b); in two cases there was general softening of the cerebral cortex (Courville, 1960 b); in two others, hydroencephaly had taken place. There were five cases of chronic cystic degeneration of the cerebral white matter. In two others the infantile form of diffuse sclerosis was the obvious cause. In all there were 15 cases in this group.

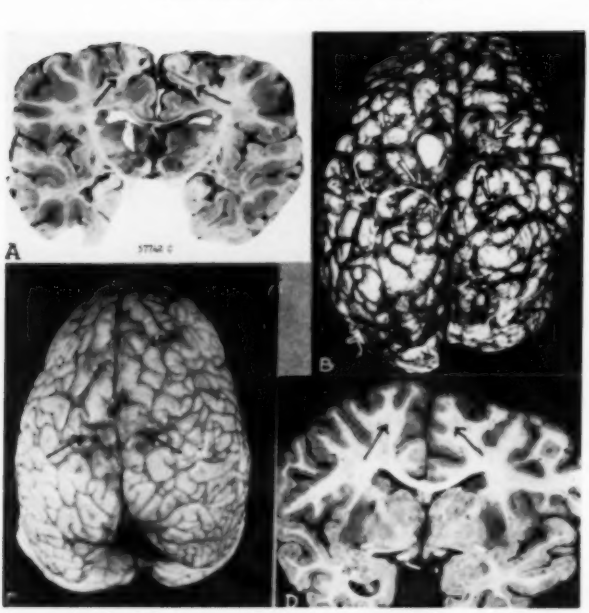

Fig. 4. Cerebral lesions causing spastic paraplegia. A. Nodular atrophy in upper motor area. B. Atypical development upper motor cortex (microgyria) bilaterally. C. Meningeal hemorrhagic staining without gross cortical changes over upper motor area following thrombosis of superior longitudinal sinus. D. Normal appearing cortex and subcortex but a local cell loss and gliosis following meningitis.

Paraplegia. Of this fairly common clinical type of motor disability, otherwise known as spastic paraplegia (Little's disease), there were only six cases with clear enough clinical pictures to warrant evaluation of the cerebral lesion found at autopsy. In one case, the lesion consisted of bilateral clefts (atypical porencephalic cysts) in the central regions involving primarily the upper end of the motor strip. A second case showed only a generalized gliosis of the white matter, whose only antecedent factor was a suppurative meningitis which had healed. The brain of a third case showed a rather generalized cortical atrophy. The other three cases demonstrated what is usually suspected to be the causative lesions, namely focal microgyria involving the upper part of the precentral gyrus. It is known (Denny-Brown, 1945) that this syndrome is also observed in cases in which it is associated with choreo-athetosis incident to alterations in the corpus striatum.

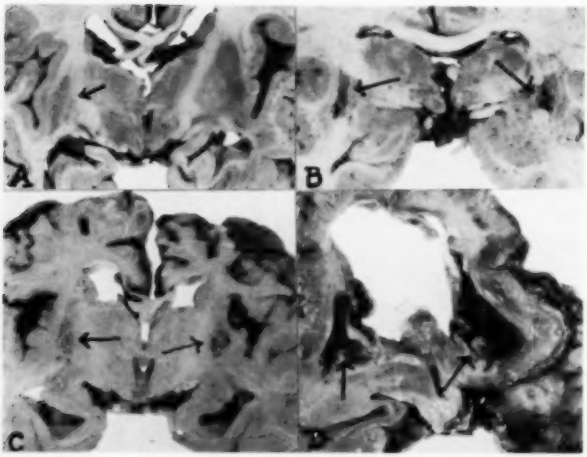

Fig. 5. Lesions of the basal ganglia. A. Unilateral atrophy of lenticular nucleus. B. Bilateral cystic degeneration of lenticular nucleus. C. Focal microcystic change associated with marked degree of nodular cortical atrophy. D. Total bilateral softening of lenticular nuclei in case of subtotal cerebral softening from paranatal circulatory disturbance.

Chorco-athetosis. A goodly number of the brains of cerebral palsied children show gross atrophy, scar formation, and cystic degeneration of the lenticular nucleus and caudate nucleus (corpus striatum). In addition, three cases of status marmoratus and one case of status dysmyelinisatus have been studied. Unfortunately, in the cases showing this group of lesions, as well as those showing status marmoratus, the clinical history was so deficient that no clear picture of hyperkinetic phenomena was elicited. This group is now undergoing a restudy with a more critical review of the clinical records to determine if such phenomena were actually visualized. It is recognized, of course, that in many such instances, any hyperkinetic activity is obscured or actually held in check by an overwhelming spasticity.

Conclusion of the Problem. As suggested by the data here furnished, variations in structure and therefore in physiology of brain-damaged children imply that a correct evaluation of the diagnosis in many cases of cerebral palsy is not an easy matter. It is probably easiest to the novice who has recently read a book on the subject; it becomes more difficult as the experience of the examiner widens and deepens.

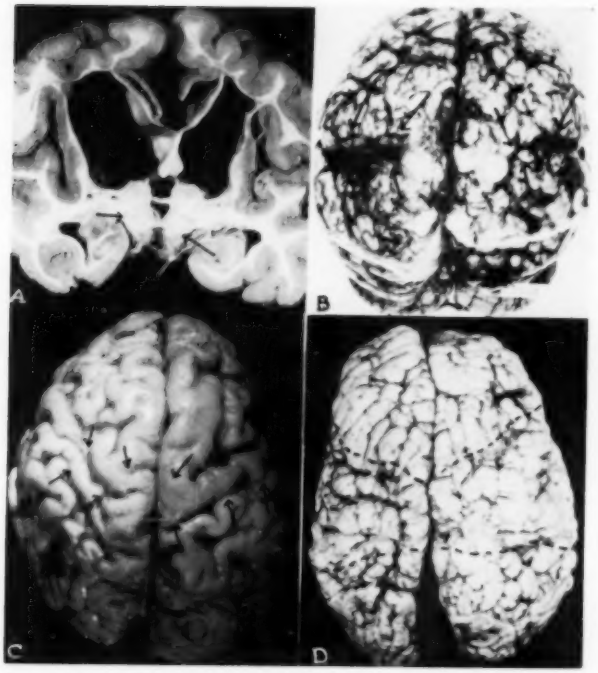

Fig. 6. Cerebral lesions causing quadriplegia. A. Advanced cortical change with marked reduction in cerebral white matter and gross ventricular dilatation. Note practically total absence of cerebral peduncles (arrows). B. Bilateral malformations (cerebral clefts) in motor cortex. C. Atypical morphogenesis of motor cortex, with macrogyria right motor cortex and irregular atrophy of the left. D. Bilateral precentral and postcentral nodular cortical atrophy.

THE GENERAL PROBLEM OF CLINICAL DIAGNOSIS

This presentation of some of the variations in the nature and degree of the numerous pathological lesions often present in the brain of a person with cerebral palsy, as well as their clinical course, makes it evident that an exact lesion diagnosis during life may constitute an extremely difficult problem. This is especially true during the early months or years of life in case of a quiescent lesion (such as a congenital malformation) or one which has not yet reached its end-stage (nodular cortical atrophy). In case of a minor lesion the diagnosis cannot be achieved even after a careful history has been taken, a critical neurological examination has been done, and electroencephalography, pneu-

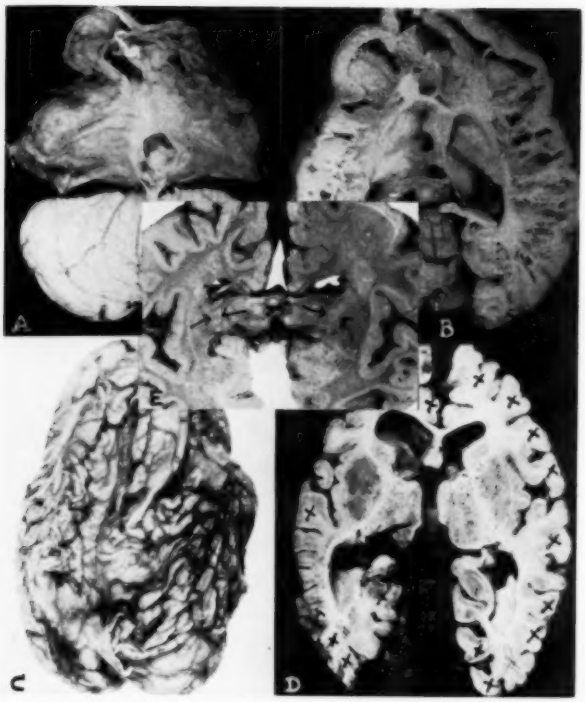

Fig. 7. Cerebral lesions causing quadriplegia with extensor rigidity. A. Hydroencephaly with total destruction of the motor system. B. Central cystic degeneration of infancy with almost total destruction of the cerebral white matter. C. Subtotal softening of the cerebral hemispheres due to paranatal circulatory disorder. D. Widespread cortical degeneration (Alpers' disease). E. Infantile case of diffuse sclerosis with widespread demyelination of white matter. Note absence of motor fibers in internal capsule.

moencephalography, and perchance, angiography have been completed. It therefore becomes futile to hope that one can always predicate on a clinical basis alone what type of brain lesion underlies the picture of cerebral palsy.

What, therefore, is to be sought from a careful examination during life? The following worthwhile objectives are to be sought: It is important to know enough about the paralyzed child to give the family some concept of prognosis. It is helpful in so doing to secure their more complete cooperation. Usually a complete prognosis cannot be made accurately in the first year of life, or even in the entire period of infancy. The "yardstick" of observation is a wise precaution to use before

any dogmatic stand is taken. This objective becomes increasingly important in the fourth, fifth, and sixth years of life. By this time a more complete survey of the entire problem is advisable.

It is helpful to determine whether rehabilitation is possible or worthwhile. This is obviously useless if the course of the disorder has been progressively downhill, as is true in the group of progressive cerebral softening observed during the first three years of life. Detailed training in useful functional activities is not so important when the patient is progressively losing what little function he has. Rehabilitation is also useless if the degree of mental deficiency present precludes any cooperative effort on the part of the child.

A most important objective in critical study of a given case of cerebral palsy is evaluation of the type and degree of motor disability in order to determine appropriate physical therapeutic measures. This study should begin early in infancy to prevent deformities and to train appropriate groups of muscles for subsequent utilization.

Another important objective of superlative clinical efforts in diagnosis is a determination of the possible etiology of the condition. Even a prolonged search is often well repaid with valuable information. There should be kept in mind the association of this possible causative factor with the ultimate lesion of the central nervous system when the case has run its clinical course.

If it is desirable to push diagnostic procedure to this point, a pneumoencephalogram is often helpful in showing the extent and location of damage to nervous tissues (especially in cases of cerebral cortical atrophy) and in demonstrating gross congenital defects. This test is also useful as a prognostic factor. For example, the prognosis would naturally be much better in the case of a normal appearing brain than it would in cases of gross cortical defects.

SUMMARY

The assumption that a complete study of the clinical aspects of a given case of cerebral palsy is sufficient for lesion diagnosis of such a case is not borne out by comparing the lesions found at autopsy with the diagnoses that have been made during life. Failure of this dictum seems to come particularly in cases of cerebral palsy which have followed anoxia at the time of birth. The essential reason is that anoxia can produce in itself a con-

siderable variety of lesions or a combination of lesions (lesion complexes). This makes uncertain not only the exact cause as to what has taken place to produce such a lesion, but also the cause of distribution of the changes in the cortex centrum or basal ganglia. Cases in which a lesion diagnosis can be anticipated with some degree of certainty are those in which a definite etiological factor can be established by association with a specific onset of the palsied state. In such cases the pattern is fairly well-defined and it is possible to suspect what will be found at autopsy. The essential reason for studying these cases with a great deal of care is not so much to satisfy the ego of the physician as it is to give the parents some estimated prognosis. This will determine whether the child merits continued attempts at rehabilitation and whether there is a type of motor disorder which can be remedied by known physical therapy measures. It will also form a basis for study when the brain lesion ultimately comes for verification.

The clinician, therefore, should not feel terribly disturbed if his lesion diagnosis does not correspond exactly with lesions found at autopsy. However, if he has done his work well and has made an effort to establish a cause for the disorders, he will be in a position to utilize the findings at autopsy in coming to a better understanding of the exact causation of the disease and in determining something of its evolution.

REFERENCES

Courville, C. B.: Ultimate residual lesions of antenatal and neonatal asphyxia. Their relation to certain degenerative diseases of the brain appearing in early life. Am. J. Dis. Child. 84: 64-78 (July) 1952.
—: Long survival with hemiplegia incident to paranatal anoxia. Case of cerebral spastic state with death from cardiac failure at eighty years of age. Bull. Los Angeles Neurol. Soc. 18:110-115 (June) 1953.
—: Residual cerebral lesions after thrombosis of the superior longitudinal sinus. Review of the literature and report of case. Bull. Los Angeles Neurol. Soc. 23:160-170 (Dec.) 1958.
—: Antenatal and paranatal circulatory disorders as a cause of cerebral damage in early life. J. Neuropath. & Exper. Neurol. 18:115-139 (Jan.) 1959.
—:Venous channel thrombosis as a possible cause of cerebral paralysis of early life. Arch. Pediat. 76:129-153 (April) 1959.
—: Structural alterations in the cerebellum in cases of cerebral palsy. Their relation to residual symptomatology in the ataxic-atonic group. Bull. Los Angeles Neurol. Soc. 24:148-165 (Sept.) 1959.
—: Central hemorrhagic encephalopathy in early infancy. Neurology 10:70-80 (Jan.) 1960.
—: Syndrome of decorticate rigidity, convulsions and amentia occurring in early infancy. Review of the literature and report of six verified cases with subtotal softening of the forebrain. Bull. Los Angeles Neurol. Soc. 25:1-17 (Mar.) 1960.
—: Pathogenesis of nodular atrophy of the cerebral cortex. Arch. Pediat. 77:101-129 (Mar.) 1960.
—:Widespread softening of the cerebral gray matter in infancy. Its probable etiology in a parantal circulatory disorder. Bull. Los Angeles Neurol. Soc. 25:72-78 (June) 1960.
Denny-Brown, D.: Diseases of the Basal Ganglia and Subthalamic Nuclei, New York, Oxford University Press, 1945 revision, Vol. VI, Chap. XI, p. 261-302.
Malamud, N.: Sequelae of perinatal trauma. J. Neuropath. & Exper. Neurol. 18:141-153 (Jan.) 1959.
Schwartz, Ph.: Birth injuries of the newborn. Arch. Pediat. 73:429-50 (Dec.) 1956.
Young, E. and Courville, C. B.: Central softening of the brain in infancy. Its possible relation to chronic cystic degeneration of the cerebral white matter. (In press.)

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Thrombocytopenic Purpura Complicating Epidemic Parotitis in a Child

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EPIDEMIC parotitis (mumps) is a common disease of infancy and childhood. Complications of this disease entity are rare in children. Of the complications, meningo-encephalitis, epididymo-orchitis, oophoritis, and pancreatitis are the most frequent. In making a complete review of the standard pediatric textbooks it was found that thrombocytopenic purpura was not listed as a complication of mumps. In reviewing the literature only three cases of thrombocytopenia due to mumps were found. The cases occurred in adults and were reported by Kolars and Spink.[1]

This case is reported for three reasons: (1) It is believed that this is the first case reported in the literature of thrombocytopenic purpura in a child occurring as a complication of epidemic parotitis. (2) It seems important to increase awareness of physicians that thrombocytopenic purpura can occur as a complication of mumps in childhood. (3) It is important to point out the fact that although steroids have a definite place in thrombocytopenic purpura, recovery can take place without their being used.

CASE REPORT

D.R.P. an 11 year old white male was first seen on the Emergency Service of Kern County General Hospital, Bakersfield, California, April 16, 1960 for a small mass under the right mandible of 3 days duration.

Past history revealed that the patient had had repeated asthmatic attacks, scarlet fever, measles, chicken pox, and influenza. He had also had an appendectomy.

PAST HISTORY

On April 14, 1960, he complained of headache and was given aspirin (5 grains). Mother stated that he had an attack of asthma a short time after taking the aspirin. On April 15, 1960, the

mother noticed swelling of both jaws and the patient began complaining of pain in his jaws on this date.

On April 15, 1960, a rash resembling a heat rash was noticed on the back and buttock. (These were probably petechiae). On April 15, 1960, and April 16, 1960, the patient brought up blood after coughing. Epistaxis began on April 16, 1960. Aspirin (5 grains) was given without an asthmatic episode occurring.

On this date the patient was seen by a private physician. At this time he had a large clot in his throat secondary to epistaxis. Temperature taken while in the doctor's office was 101° F.

The rash was petechial and purpuric. The patient was referred to Kern County General Hospital with a diagnosis of thrombocytopenic purpura due to mumps.

Physical examination done on the Emergency Service revealed a well developed, slightly obese, 11 year old white male. Temperature was 103.6° F. Pulse 120/minute and respirations 24/minute.

Head, eyes, ears, and neck were normal.

Nostrils: Dried and fresh blood could be seen in the nostrils.

Throat: Tonsils were moderately enlarged but no infection was seen.

Face: Massive swelling of both mandibular areas and both parotoid areas was observed. Bluish and purplish discoloration of the swollen areas was seen.

Neck: Bluish and purplish discoloration seen in mandibular and parotid areas was also seen on the neck.

Chest: Normal in size and shape. Heart was not enlarged to percussion. Heart rate was rapid and no murmurs were heard. Lungs were clear to auscultation and percussion.

Abdomen: Normal in size and shape. No masses were palpated. Surgical scar was seen in right lower quadrant.

Genitalia: Normal for age.

Extremities: Normal in size and shape. Ecchymotic lesions were seen on legs, and arms.

Skin: Petechiae were seen in scattered areas of the back, buttocks, thighs, and legs. Ecchymotic lesions were seen on the buttocks, arms and legs.

Impression: (1) Epidemic parotitis. (2) Thrombocytopenic purpura due to epidemic parotitis.

Laboratory Findings: On April 16, 1960, the hemoglobin concentration was 13.9 gm./100 cc. with 5,000 leukocytes/cu. mm. There were 23 lymphocytes, 14 monocytes, 58 polymorphonuclear leukocytes, 3 stabs, and 2 myelocytes in 100 leukocytes. There were 4,920,000 erythrocytes/cu. mm. This platelet count was 18,000/cu. mm.

On April 16, 1960, urinalysis revealed a specific gravity of 1.011. Albumin and sugar were negative. There were 1-3 white blood cells and 5-10 red blood cells per high-powered field.

On April 18, 1960, laboratory tests were done with the following results:

TABLE 1

Clot Retraction	Bleeding Time	Clotting time	Prothrombin Consumption	Prothrombin time	Prothrombin Generation	Antihemophilic Globulin	Plasma Thromboplastin Component
No retraction in 30 seconds.	1¼ minutes	4½ minutes	Normal	15 seconds (90% of control)	Normal	Normal	Normal
Serum volume 20%							
Extremely soft clot							

TABLE 2

Summary of the laboratory tests and patient's condition during hospital stay:

Date	*Results of laboratory tests*	*Comments*
4/17/60	No tests done.	Did not sleep well previous night. Complains of pain in mandibular areas. Malaise.
4/18/60	See table 1. Platelet count 64,000/cu. mm.	No bleeding from mouth. Uncomfortable in general.
4/19/60	Platelet count 37,000/cu. mm.	Patient feels better. Increased swelling of mandibular areas. Bluish discoloration still prominent in mandibular area. Purplish discoloration seen behind right auricle. Had black formed stool. Stool to laboratory for blood.

4/20/60	Serum amylase 362 (Somogyi units); Hemoglobin concentration 10.6 gram/100cc.; 3,100 leukocytes/cu. mm. Lymphocytes 45% Polymorphonuclear 39% Monocytes 7% Eosinophils 2% Juveniles 1% Stabs 6% *Erythrocyte fragility*. Hemolysis began in 0.48% and was complete in 0.34% saline. Platelet count 8,000/cu. mm.	Seemed improved, in general. Complained of pain in right leg. Parotid swelling noticed.
4/21/60	Platelet Count 8,000/-cu. mm.	Complained of pain in both legs. Swelling in mandibular and parotid areas was less. Blood drawn for complement fixation.
4/22/60	No L.E. cells were discovered when appropriate smears of peripheral blood were examined. Platelet count 30,000/cu. mm.	Less swelling of face. Much better Petechiae over buttocks and thighs are fading.
4/23/60	Hemoglobin concentration 11.3 gm./100cc.; Hematocrit 35% Platelet count 54,000/cu. mm.; Test for occult blood in stool was positive.	Petechiae over legs remain essentially unchanged. Further recession of facial swelling. Bluish discoloration of face and neck persists. Complained of pain in right hip and ankle. Good appetite and good stools. Petechiae over buttocks and thighs are fading.
4/24/60	Platelet count 80,000/-cu. mm.	No problem.
4/25/60	Hemoglobin concentration 10.9 gm/100 cc. Hematocrit 34%. Platelet count 138,000/cu. mm.	Better. Complains of pain in right hip and right ankle. Also complains of pain in left leg.
4/26/60	Hemoglobin 11.5 gm/100 cc.; Hematocrit 38%; 5,600 leukocytes; Lymphocytes 46% Polymorphonuclear leukocytes 47% Monocytes 6% Stabs 1% Platelets 128,000/cu. mm.	Had headache last night. Complains of pain in right ankle. Bluish discoloration of face persists. Petechiae on buttocks and thighs are almost gone although some are seen on lower legs and ankles. Purpuric lesions are still present on right thigh and scattered areas of body but they are fading.
4/27/60	Hemoglobin concentration 11.5 gm/100 cc. Hematocrit 37%; Platelets 100,-000/cu. mm.	No problem.
4/28/60	Hemoglobin concentration 11.8 gm/100 cc. Hematocrit 36%; Platelets 97,-000/cu. mm.	No problem.

4/29/60	Hemoglobin concentration 11.8 gm/100 cc. Hematocrit 37%; Platelets 108,000/cu. mm.	No problem. Blood drawn for complement fixation.
4/30/60	Hemoglobin concentration 11.5 gm/100 cc. Hematocrit 36%; Platelets 147,000/cu. mm.	All petechiae are gone. Few purpuric lesions left on right thigh in iliac regions, sternal area, and parotid area.
5/1/60		No problem.
5/2/60		Slight bluish discoloration of parotid area persists. Seems very well.
5/3/60	Hemoglobin concentration 12.2 gm/100 cc. Hematocrit 40%; Platelets 140,000/cu. mm. Bone marrow studies revealed an E.M. (erythroid-myeloid) ratio of 1:4. There were rather large erythroid cells. The myeloid series appeared unremarkable. Megakaryocytes were present. Platelets were reduced in number.	Bone marrow aspiration done using right ilium.
5/4/60		No problem.
5/5/60		Looks very fine. Parotid areas are still very slightly blue. Discharged.

Patient was seen by his private physician on May 11, 1960. At this time ecchymosis was noted in the right mandibular area and over the sternum. He complained of pain in the right leg. He did not seem to be entirely well so his physician limited his activities. At this time the hemoglobin concentration was 13 gm/100 cc. Hematocrit was 45%. There were 46 lymphocytes, 52 polymorphonuclear leukocytes and 2 eosinophils in 100 leukocytes. There were 6,850 white blood cells/cu. mm. Platelet count was 190,000/cu. mm.

The blood drawn April 21, 1960 and April 29, 1960, for complement fixation (mumps) was run on May 18, 1960. The first specimen was 1:16 and the second 1:64 which indicates positive complement fixation for mumps.

When seen by his private physician on June 7, 1960, he was entirely well. There was no evidence of purpura. His platelet count at this time was 186,000/cu. mm. He has been allowed full activities and will be followed by his private physician.

DISCUSSION

The various purpuras may be divided, for clinical purposes, into two major groups: (1) Thrombocytopenic purpura and (2) nonthrombocytopenic purpura.

Thrombocytopenic purpura may be further divided into idiopathic thrombocytopenic purpura and secondary thrombocytopenic purpura and nonthrombocytopenic purpura may be further divided into anaphylactoid or allergic purpura, and secondary thrombocytopenic purpura.

This paper is concerned with secondary thrombocytopenic purpura because the purpura and thrombocytopenic were secondary manifestations of epidemic parotitis.

No statistics are available to indicate the incidence of thrombocytopenic purpura complicating mumps. This is the fourth case to appear in the literature. The fact that no other cases have been reported does not necessarily mean that there have not been more such cases, but could mean that for one reason or another the physicians seeing the patients did not report the cases.

Although no mention was made of thrombocytopenic purpura in association with mumps in the standard pediatric textbooks[2,3,4,5,6], mention was made of other exanthematous diseases such as chicken pox, measles, and rubella in association with thrombocytopenic purpura.

Other infectious diseases have been reported in association with thrombocytopenic purpura. Clement and Diamond[7] in 1953 reviewed cases of 140 infants and children with purpura. 96 of these patients had thrombocytopenic purpura and 44 had nonthrombocytopenic purpura. 65 of the 96 patients with thrombocytopenic purpura had acute infection associated with the onset of the purpura. In all but 7 of the 65 patients with thrombocytopenic purpura upper respiratory infections were present. The 7 patients who did not have upper respiratory infection had rubella, chicken pox, infectious mononucleosis and pyelonephritis. Meningococcemia, pneumonia, measles, streptococcal and other types of septicemia and tuberculosis have been associated with thrombocytopenic purpura. Ferguson[8], reported on rubella as a cause of thrombocytopenic purpura. He states only 17 cases had been accurately described previously. He reported on 3 cases to make 20 cases of rubella causing thrombocytopenic purpura.

The etiology of thrombocytopenic purpura is not clear. Some theories of its causation are: (1) Reduced formation of platelets from the megakaryocytes. (2) Increased platelet destruction by the spleen or by a platelet-destroying anti-body produced by an abnormal immune mechanism, and (3) Impaired capillary wall strength, due to defective intercellular cement substance.

In discussing the complications of mumps, Kolars and Spink[1] mentioned that direct invasion of the tissue by virus may be responsible for the inflammatory reactions that occur and that a state of acquired hypersensitivity may also be responsible for the complications associated with mumps.

Steroid therapy was useful in treating the 3 patients reported by Kolars and Spink[1]. In two of the patients steroids were insufficient to correct the platelet deficiency but controlled the bleeding tendency. In the third patient steroid therapy controlled orchitis and the thrombocytopenic purpura. In the case reported in this paper it was decided to withhold steroid therapy if no further bleeding took place. In this way it could be shown that the remission was spontaneous provided steroids were not used. On April 20, 1960, and April 21, 1960, when the platelet count was 8,000/mm on two successive days it was felt that steroids should be used. However, since the patient had had no bleeding and since his condition seemed better, it was decided to wait one more day. It was a relief to note the platelet count, 30,000/cu. mm. on April 22, 1960. The platelet count rose after that to 54,000/cu. mm. on April 23, 1960, and 80,000/cu. mm. on April 24, 1960. Since the platelet count was rising there seemed to be no need to use steroids.

Since the possibility of lupus erythematosus must be considered in patients with thrombocytopenic purpura, examination of appropriately preparated peripheral blood for L.E. cells was done. No L.E. cells were seen.

Since aplastic anemia and leukemia are also diagnostic possibilities, bone marrow studies were done. Megakaryocytes were present and erythroid-myeloid ratio was normal. Reading was compatible with diagnosis of thrombocytopenic purpura.

SUMMARY

1. A case is reported of an 11 year old male who had thrombocytopenic purpura as a complication of mumps. This is believed to be the only case reported of this entity in a child.

2. Although the efficacy of steroids in the management of thrombocytopenic purpura has been documented spontaneous remission can occur if they are not used. Discretion should be exercised in using steroids in thrombocytopenic purpura.
3. The incidence of thrombocytopenic purpura complicating mumps cannot be determined until more data are available.
4. Some theories as to the pathogenesis of thrombocytopenia are listed.
5. Some other infectious diseases associated with thrombocytopenic purpura are mentioned.

REFERENCES

1. Kolars, C. P. and Spink, W. W.: Thrombocytopenic Purpura As a Complication of Mumps. J.A.M.A. 168:2213-2215, 1958.
2. Nelson, W. E.: Textbook of Pediatrics. 7th Edition. Philadelphia, 1959. W. B. Saunders Company.
3. Holt, L. E. Jr., and McIntosh, R.: Pediatrics. 12th Edition. New York, 1953. Appleton-Century-Crofts, Incorporated.
4. Grulee, C. G. and Eley, R. C.: The Child in Health and Disease. 2nd Edition. Baltimore, 1952. The Williams and Wilkins Company.
5. Paterson, D. & McCreary, J. F.: Pediatrics. 1st Edition. Philadelphia, 1956. J. B. Lippincott Company.
6. Cecil, R. L. & Loeb, R. F.: A Textbook of Medicine. 10th Edition. Philadelphia, 1959. W. B. Saunders Company.
7. Clement, D. H. & Diamond, L. K.: Purpura in Infants and Children. A.M.A. J. Dis. Child. 85:259-278, 1953.
8. Ferguson, A. W.: Rubella As a Cause of Thrombocytopenic Purpura. Pediatrics. 25:400-408, 1960.

APPRECIATION

I wish to express my appreciation to Dr. Agnes D. Tarr of Taft, California for sending this patient in for admission to Kern County General Hospital, thereby making it possible to report this case.

She has taken care of this patient since his discharge from the hospital.

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Management of Underweight Infants and Children

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ANOREXIA and inability of infants and children to gain weight are common problems encountered by many physicians. Causes of such problems may evolve from allergy, metabolic disturbances, nutritional deficiencies, prematurity, or organic involvement. Specific tests should be performed to rule out many of these causes.

With premature infants it is obligatory to use a safe therapeutic agent that stimulates weight gain in order to carry the youngsters through the dangerous phase of arrested growth during the first three weeks of life. Older children with anorexia, if not corrected, may develop psychologic disorders usually precipitated by parents during mealtime battles of forced feedings. When this occurs, the child may resist food with vomiting or with complaints of pain in the abdominal region. Specific diets, tonics and other appetite stimulants are prescribed but fall short of their goal by lacking anabolic action, so necessary for biologic stimulation to appetite and weight gain.

Recently, a new approach to the problem of weight gain was observed by the author while visiting the pediatric clinic of the Child Jesus Children's Hospital, Rome, Italy. Doctor Bettolo, clinic director, demonstrated the results of a new anabolic stimulant, nandrolone phenpropionate,** in treating underweight and malnourished children for a period of three months. He noted persistent weight gain associated with improved appetite, vitality, and strength which did not reverse after discontinuance of therapy. Nandrolone phenpropionate stimulates the protein-anabolic processes, previously depressed, without evidence of premature ossification of the skeletal system or causing virilism.

Jonxis and Maats[1] in their study concluded that nandrolone phenpropionate increased weight in children where dietary measures and tonics failed. Ungari and Rossoni[2] treated ten dystropic

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infants and 328 older children, 2 to 13 years of age, with nandrolone phenpropionate. All patients gained weight and showed greater vitality. In some of the older children an improvement in intellectual ability was observed. Other reports[3,4] attest to its potent anabolic action with virtual freedom from side reactions, so that it can be safely administered to infants and children where weight gain is desired.

It has long been recognized that androgens possess the ability to promote protein anabolism which is of inestimable value to physicians treating underweight children; however, androgens have other effects which are often undesirable. From testosterone to norethandrolone there are many reports giving evidence to such side effects as virilism, priapism, progestational effects, water retention, and derangement of liver function.[5,6,7,8]

From reports abroad and in this country[9,10,11] proclaiming the potent anabolic effect of nandrolone phenpropionate without appreciable androgenicity, we decided to administer this preparation in our clinic to determine its efficacy in the treatment of underweight infants and children.

METHOD

A total of 44 patients were divided into three groups; group I, 13 premature infants, group II, 14 children from 1.5 to 6 years of age, and group III, 17 children from 7 to 13 years of age.

In group I, birth weight of five pounds or less was the criterion for prematurity. Dosage was 12.5 mg. (0.5 cc.) intramuscularly (buttock) on the 2nd, 4th, 8th and 10th week of life. Nine other premature infants not treated with test-substance were used as control for weight comparisons. The birth weight of the treated and control group of infants were recorded prior to instituting therapy. Subsequent weighings were made daily for five weeks, then weekly thereafter. All infants in the treated and control group received the routine formula feedings.

In group II and III the dosage was 25 mg. (1 cc.) intramuscularly every two or four weeks, as indicated. The duration of therapy ranged from 4 to 24 weeks.

Our objectives, in all groups, were to observe weight gain and any or all of the following; change in appetite, physical activity, mental alertness, premature closure of the epiphyses, enlargement of the clitoris, and priapism.

Weight changes observed in group II and III were compared to the Average Standard Weights by Age and Sex as published in Pediatric Nursing.[12] No attempts were made to regulate the children's diet with the exception of recommending a high-protein intake with a balanced fat-carbohydrate ratio.

Our technic of drug administration was to draw up dose volume into the hypodermic syringe with a large needle (19 gauge) to minimize bubble formation and then substitute a smaller needle (22 gauge) suitable for intramuscular injection to infants and children. All patients in our study were unselected and regardless of sex or weight (group II and III) were categorized according to age. The criteria were that all patients be devoid of diseases and their lack of ability to gain weight be from a constitutional etiology.

RESULTS

In group I the composite weight gain recorded from nandrolone phenpropionate therapy in premature infants is summarized in table I.

TABLE I

Average Weight Gain - Premature Infants

Age	Control Group (9)	Treated Group (13)	Dosage
Birth	4.58 lbs.	4.53 lbs.	-
1st week	4.00 lbs.	3.94 lbs.	-
2nd week	4.12 lbs.	4.10 lbs.	12.5 mg.
3rd week	4.29 lbs.	4.47 lbs.	-
4th week	4.55 lbs.	4.83 lbs.	12.5 mg.
5th week	4.86 lbs.	5.45 lbs.	-
6th week	5.17 lbs.	6.44 lbs.	-
7th week	5.46 lbs.	7.50 lbs.	-
8th week	5.78 lbs.	8.49 lbs.	12.5 mg.
9th week	6.37 lbs.	9.39 lbs.	-
10th week	6.83 lbs.	10.30 lbs.	12.5 mg.

Comparison of data shows that after 10 weeks of therapy the treated group of infants gained 5.8 pounds above their birth weight; whereas, the control group of infants gained only 2.4 pounds. This represents a 58.7 per cent increase in weight as depicted in graphs I and Ia. Sucking reflex and desire for feedings were more pronounced in the treated group of infants. Initial stimulation of appetite with nandrolone phenpropionate accelerated weight gain in the treated infants.

Composite of weight gain recorded for the children in group II (table II) shows an average of 5.7 pounds increase in weight which represents a 16.7 per cent increase over their initial weight before commencing therapy. The same analysis of group III (table III) shows an average weight increase of 7.1 pounds or a 12.3 per cent increase over the children's weight before instituting treatment.

TABLE II

Weight Gain - Children 1½ yrs. to 6 yrs. of Age *

Case #	Age & Sex	Weight in Pounds Before	Weight in Pounds After	Dosage & Frequency	Duration of Therapy	Av. Std. by Age in Pounds*
L.S.	1½ yrs. (F)	20.5	24.2	12½ mg. (2 wks.)	8 wks.	22.6
S.T.	3 yrs. (M)	27.1	31.5	12½ mg. (2 wks.)	10 wks.	31.2
M.W.	4 yrs. (F)	31.0	34.5	25 mg. (2 wks.)	8 wks.	34.0
C.D.	4½ yrs. (M)	31.0	37.0	12½ mg. (2 wks.)	10 wks.	38.1
S.G.	4½ yrs. (F)	29.2	35.8	25 mg. (4 wks.)	12 wks.	36.9
N.S.	5 yrs. (F)	34.2	39.0	12½ mg. (3 wks.)	21 wks.	39.8
G.T.	5½ yrs. (F)	37.0	45.5	25 mg. (2 wks.)	10 wks.	41.6
J.D.	5½ yrs. (M)	36.2	39.5	25 mg. (4 wks.)	12 wks.	43.2
C.F.	6 yrs. (M)	39.0	43.5	25 mg. (2 wks.)	6 wks.	43.5
W.F.	6 yrs. (M)	36.5	40.7	25 mg. (2 wks.)	6 wks.	43.5
J.B.	6 yrs. (F)	41.2	49.0	25 mg. (2 wks.)	18 wks.	42.0
S.T.	6 yrs. (F)	40.2	46.8	25 mg. (4 wks.)	20 wks.	42.0
R.D.	6½ yrs. (M)	34.5	41.8	25 mg. (4 wks.)	16 wks.	45.2
S.R.	6½ yrs. (M)	40.2	48.8	25 mg. (2 wks.)	14 wks.	45.2

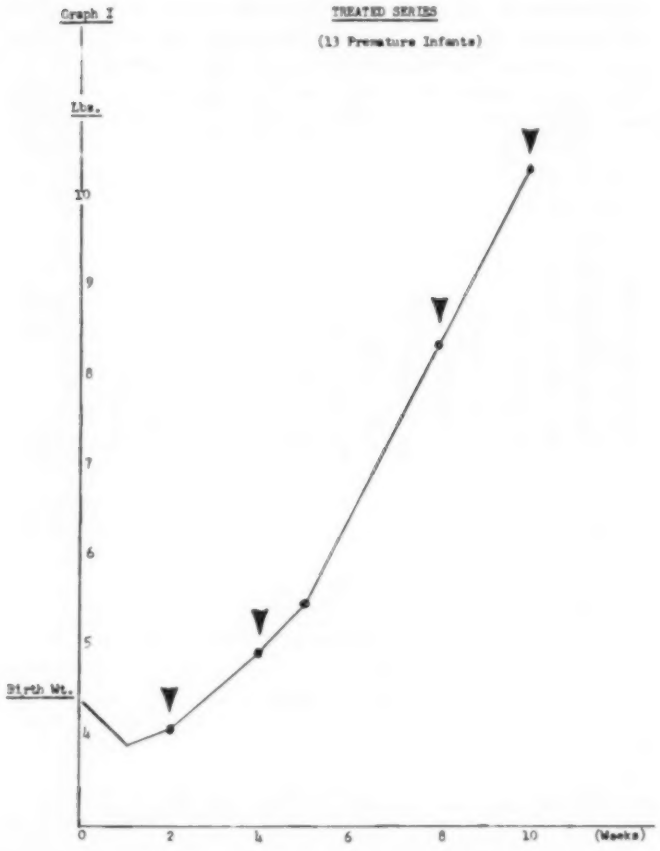
*BENZ, G.S.: Pediatric Nursing, C.V. Mosby., 1948, p. 168.

TABLE III

Weight Gain - Children: 7 yrs. to 13 yrs. of Age

Case #	Age & Sex	Weight in Pounds Before	Weight in Pounds After	Dosage & Frequency	Duration of Therapy	Av. Std. by Age in Pounds*
C. B.	7 yrs. (M)	43.5	47.5	25 mg. (2 wks.)	16 wks.	47.0
M. B.	7½ yrs. (M)	43.2	47.5	25 mg. (2 wks.)	10 wks.	49.2
J. W.	8 yrs. (F)	50.7	55.0	25 mg. (2 wks.)	10 wks.	49.5
K. L.	8 yrs. (M)	46.5	51.8	25 mg. (2 wks.)	10 wks.	51.4
S. R.	8 yrs. (M)	50.5	51.5	25 mg. (4 wks.)	8 wks.	51.4
C. W.	8 yrs. (F)	53.0	56.7	25 mg. (3 wks.)	15 wks.	49.5
S. L.	9½ yrs. (M)	49.5	57.2	25 mg. (4 wks.)	24 wks.	59.6
S. D.	9½ yrs. (F)	51.0	55.5	25 mg. (2 wks.)	6 wks.	56.6
P. G.	10 yrs. (M)	49.5	56.2	25 mg. (4 wks.)	20 wks.	62.3
B. M.	12 yrs. (M)	60.0	73.0	25 mg. (4 wks.)	16 wks.	73.0
J. P.	12 yrs. (F)	65.0	76.0	25 mg. (2 wks.)	12 wks.	74.1
L. K.	12 yrs. (M)	65.0	75.0	25 mg. (2 wks.)	10 wks.	73.0
K. O.	12 yrs. (F)	63.5	73.5	25 mg. (4 wks.)	20 wks.	74.1
E. K.	12½ yrs. (F)	69.2	76.0	25 mg. (4 wks.)	8 wks.	78.7
J. L.	13 yrs. (M)	74.0	87.0	25 mg. (4 wks.)	20 wks.	80.6
L. K.	13 yrs. (F)	76.8	85.5	25 mg. (2 wks.)	12 wks.	83.8
J. P.	13 yrs. (M)	70.0	73.0	25 mg. (2 wks.)	4 wks.	80.6

*BENZ, G. S.: Pediatric Nursing, C. V. Mosby Co., 1948, p. 168.

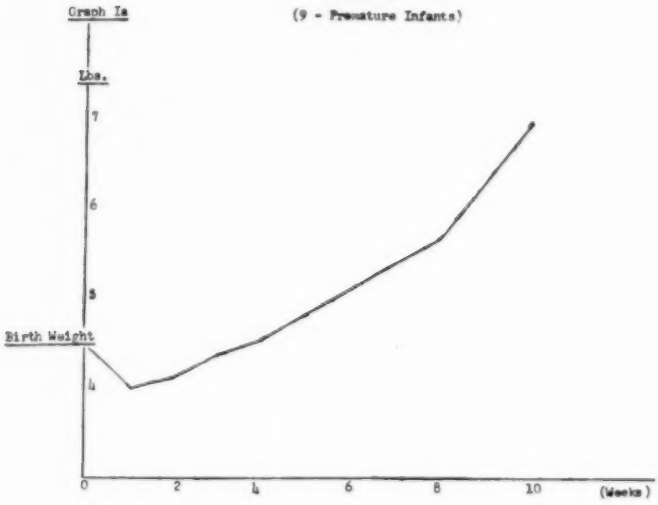


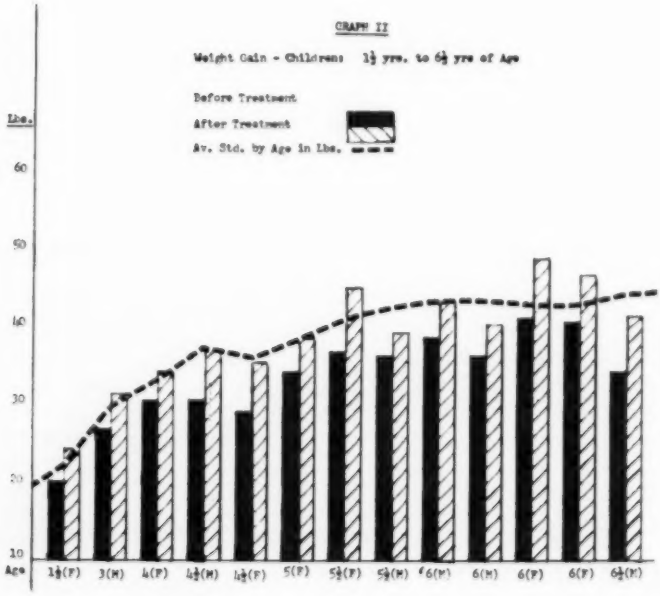
Comparison of the average weight gain by the children in group II and III with the Average Standard Weights by Age and Sex, we find group II with a 13.1 per cent and group III with a 10.2 per cent below their normal weight before treatment. Comparison, after an average duration of treatment of 12 weeks, reveals group II and III to have an increase in weight above normal standards of 1.7 per cent and 0.5 per cent, respectively.

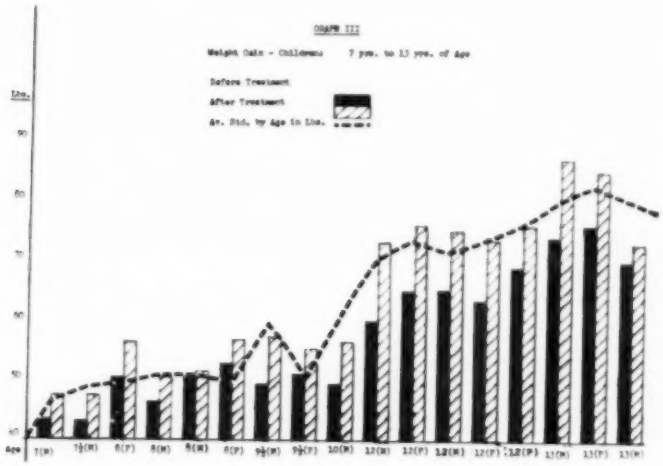
The data recorded in group II and group III are shown in graph II and graph III, respectively.

CONTROL SERIES

(9 - Premature Infants)







A definite improvement in eating habits and appetite associated with greater physical activity was observed in all children after the first week of treatment with nandrolone phenpropionate. There was no evidence of premature closure of the epiphyses or bone ossification as demonstrated by roentgenographic studies taken before and after therapy. No signs of virilism occurred in the male or female child. The only side effects noted were two instances of post-injection induration which cleared spontaneously.

SUMMARY

A total of 44 patients, divided into three groups according to age, were treated with nandrolone phenpropionate for a period of from 4 to 24 weeks. Group I, premature infants, averaged 58.7 per cent increase in weight over the control group of infants. Group II, children from 1.5 to 6 years of age, averaged 16.7 per cent increase in weight. Group III, children from 7 to 13 years of age, averaged 12.3 per cent increase in weight. In addition to weight gain, all youngsters had an increase in appetite, vitality and strength.

No undesirable reactions of virilism occurred. Two patients had mild induration of a transitory nature. Roentgenographic studies, taken before and after therapy, exhibited no premature closure of epiphysis or bone ossification.

CONCLUSION

Our clinical observations proved nandrolone phenpropionate to be highly effective in establishing weight gain and because of its lack of side effects it is highly recommended in preference to other 19 nor-steroids for administration to infants and children.

REFERENCES

1. Jonxis, J. H. P., and Maats, B. C.: Effect of Durabolin on Weight Increase in Children, Nederl. Tijdschr. Geneesk 101:389-392, 1957.
2. Ungari, C., and Rossoni, C.: Pediatric Use of a New Anabolic Steroid with Prolonged Action. Aggiorn, Pediatr. 9:311, 1958.
3. Lambillon, J.: Norandrostenolone Phenyl Propionate: Its Therapeutic Use in Europeans in Tropical Climates. Bruxelles-Med., 37, 1476-1482, October 6, 1957.
4. Nowakowski, H., and Parada, J.: Clinical Experience with 19-nortestosterone phenylpropionate, Deutsche Med. Wockenschrift, 34:1421, 1958.
5. Payne, R. W.: Anabolism, Appetite, and Ambition, Jo. Kentucky Acad. G. P., October, 1959.
6. Goldstein, L. S.: Norethandrolone and Reserpine—A Study of Treatment of Nervous, Underweight Children, Arch. Ped., 76:196, June, 1959.
7. Payne, R. W.: The Androgens, Okla. S. Med. Assoc., pp. 461-464, July, 1959.
8. Kory, R. C., Bradley, M. H., Watson, R. N., Callahan, R., and Peters, B. J.: A Six-Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons, Amer. J. Med., 26:243, 1959.
9. Szujewski, H. A.: A New Palliative Agent in the Management of Mammary Carcinoma, Am. Prac. and Dig. of Treatment, Vol. 10, No. 12, December, 1959.
10. Banghart, H. E.: Some Observations on Osteoporosis, Bull. Acad. Med. N. J., 5:70-76, June, 1959.
11. Sobel, J.: Clinical Study of Nandrolone Phenpropionate, Clin. Med., 7:481, 1960.
12. Benz, G. S.: Pediatric Nursing, C. V. Mosby Co., 1948, p. 168.

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Poison Control . . .

. . . CHLOROMYCETIN POISONING

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CHLOROMYCETIN poisoning is being reported with greater frequency during the past few years. In June 1960, Drs. Lambdin, Waddell, Jr., and Birdsong reported on a study of deaths which occurred during the prophylactic administration of Chloramphenicol to premature infants.†† The study clearly indicated that the potential toxicity of this drug in the premature infant is great and that the dosage commonly recommended should be reduced. They recommended that the daily dose for premature infants should not exceed 25 mg per kg of body weight and for the full term the daily dose should be 50 mg per kg of body weight. The authors also indicated the need for more careful evaluation of any drug prior to their release for administration to infants and particularly to infants in the lower weight categories.

While the number of reported cases of agranulocytosis caused by Chloromycetin has apparently decreased in the last few years, the number of reported aplastic anemia cases associated with the use of Chloromycetin has increased.

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††Lambdin, Morris A., M.D., Waddell, W. W., M.D., Birdsong, McLemore, M.D.: Chloramphenicol Toxicity in the Premature Infant, Pediatrics, Vol. 25, No. 6, pp. 935-940, June 1960.

The following case of a Chloramphenicol poisoning in a 7-year old white female, who was a patient at Mount Sinai Hospital, was reported by Dr. Donald Gribetz to the Poison Control Center. This child became ill three months prior to her admission to Mount Sinai Hospital. She presumably had then a non-diagnosed rash which may have been rubella and the mother who had a supply of Chloramphenicol gave it to the child, apparently without medical supervision, for a period of three days. The total dose administered could not be determined. Five weeks prior to admission, the patient developed purpura. A complete blood count done at this time by the family physician showed a low platelet count. She was then admitted to a hospital where a depression of all blood elements was found, and she was treated with steroids and blood transfusions. After three weeks' hospitalization, the child developed mumps and was therefore discharged from the hospital. A week later, on June 20, 1960, she was admitted to Mount Sinai Hospital for further evaluation of her original illness.

On admission here, she had ecchymoses and an enlarged liver. The initial hemogram showed a hemoglobin of 9.4 gm%, and a red blood count of 3.32 million, reticulocytes less than 0.5%, white cell count 6,250, band cells 4, segmented forms 1, lymphocytes 94, monocytes 1, platelets 12,000. A bone marrow showed hypoplasia with the granulocytic and normoblastic elements markedly reduced.

The patient was started on 5 mg of Prednisone four times a day and 50 mg of testosterone intramuscularly daily. Despite this therapy and numerous blood transfusions the child went steadily downhill. She developed hematuria, hematemesis and on August 20, 1960 she became febrile. E coli was found in her blood and she was treated with intravenous Furadantin but to no avail. She became comatose and expired on August 27, 1960.

The hematologist, Dr. Peter Vogel, was of the opinion that this patient developed an aplastic anemia secondary to Chloromycetin and expired because of E colisepsis. The autopsy was performed by Dr. Milton Helpern, Chief Medical Examiner of the City of New York. The findings were as follows:

EXTERNAL INSPECTION

The body is that of a well developed, well nourished, obese female child, appearing older than seven years. It is 4'2" tall, estimated weight about 65 pounds. Scalp hair is brown. Face is puffy and

rounded. There is a slight growth of hair on the pubes. The right labium minus is considerably swollen and the overlying skin is excoriated and slightly macerated. The tissues are indurated in this region. Eyes are brown. There is abundant subconjunctival hemorrhage which is dark red in color. There is bilateral periorbital ecchymosis which is part of a generalized purpura. The skin of the entire body is covered with numerous variable sized circular, bluish-red and blue purpuric spots up to ½" in largest dimension. There is some blackish fluid oozing from the nose. The teeth are in fairly good condition. There is slight patchy gingival hemorrhage. The mucous membranes and skin are pale. There are needle puncture marks in the antecubital fossa. The breasts show slight hypertrophy, but this is found to consist mainly of fat. Rigor mortis is complete.

On section of trunk: Panniculus light yellow in color, up to 2 cm. in thickness. Recti muscles are thin. Diaphragm fourth rib on the right, fourth space on the left. No free fluid in the peritoneal cavity. The mesenteric lymph nodes are slightly enlarged and on section show some interstitial hemorrhage. There is also some retroperitoneal hemorrhage along the aorta on both sides. No free blood is found in the peritoneal cavity. Abdominal viscera are normally distributed. The stomach presents an ecchymotic appearance due to infiltration which is interstitial within the muscular wall and also mucosal as will be described later.

Lungs: On opening into the chest, the costal cartilages are easily cut through. There is a small amount of pale thymic tissue within the superior mediastinum. Both lungs are free in the pleural cavities which contain no fluid. The surfaces of the lungs are smooth. Anteriorly and laterally they are pale. Posteriorly they show slight congestion. There are scattered small purpuric hemorrhages in the pleura and in some areas extending slightly into the parenchyma, the latter found in the right lung. The bronchi are congested. The lungs are crepitant throughout; light in weight. The cut surfaces for the most part are pale. The pulmonary vessels contain some red fluid blood which appears relatively thin.

Neck organs: Are not obstructed. The thyroid gland has a glazed appearance and is light tan in color.

Heart: Lies free in pericardial sac which contains a few cc of clear fluid. The epicardium is shiny with scattered small purpuric hemorrhages beneath its surface, both on the anterior and on the

posterior and lateral walls and also on the walls of the auricles. The chambers of the heart contain fluid blood which is homogeneous and red. The valves of the heart are flexible and natural. The fossa ovalis is closed. There are scattered dark red subendocardial hemorrhages on the left side in the interventricular septum and, on further section of the myocardium, the muscle is pale with some scattered small dark red interstitial hemorrhages, one of which is found in the upper part of the interventricular septum near the membranous portion. The aorta throughout its length is smooth and elastic. The intima is smooth and has a porcelain like translucency.

Gastrointestinal tract: The esophagus is natural. The stomach contains about 250 cc of dark red fluid blood—somewhat hemolized. The mucosa of the stomach is everywhere hemolized and infiltrated with blood and there is also blood found in the muscularis and in the submucosa. The hemorrhagic condition is found only in this viscus. It does not involve the remainder of the gastrointestinal tract. The latter contains some greenish-gray mushy content. The other part of the small bowel contains some tarry black material, evidently digested blood. The large bowel contains some greenish-black material. The mucous membranes of the small and large intestine are not remarkable.

Gall bladder: Contains about 10 cc of thick, green, viscid bile. The ductus is not obstructed.

Spleen: Is normal in size. Cuts with a sharp edge. The pulp is dark red in color and somewhat dry.

Pancreas: Is firm, pale. Lobulations well preserved.

Adrenals: Are imbedded in a considerable amount of fat. The adrenal color blends with that of the light yellow fat, is slightly darker, somewhat tawny, and the medullary layer is indistinct.

Kidneys: Are also imbedded in large fatty capsules. The fibrous capsules strip easily. The surfaces of the kidney are pale tan in color with scattered small hemorrhages visible on the surface. On section, the pelvis of each kidney is extensively infiltrated with blood and is completely obscured by this layer of infiltrated blood and free blood in the lumen. In addition the medullary rays are streaked with dark red blood, but this process is not uniform. However, there is distinct hemorrhagic streaking of these rays, the hemorrhagic line standing out in sharp contrast to the otherwise pale parenchyma. The ureters apparently are clear.

Urinary bladder: Is slightly contracted. It contains a soft blood clot of about 20 cc in volume. The mucosa is infiltrated with blood and this is most conspicuous around the trigone.

Internal genitalia: The reproductive organs: The uterus is small, infantile. The endometrium is pale. The ovaries contain some undeveloped follicles. The bone marrow of the vertebral column and also of the sternum is extremely pale, light grayish-tan in color. No red marrow noted.

On section of head: On reflecting the scalp, there is hemorrhage beneath the fascia of both temporal muscles and also in the substance of the temporal muscles. There are scattered small hemorrhages seen in the scalp, more purpuric in type. The calvarium is an 1/8" to 3/16" in thickness. On removing the calvarium and opening the dura on the left side over the cerebral hemisphere, there is a thin layer of dark red, soft clotted blood, which is adherent to the dura and stains it somewhat. Subsequently, when the brain is taken out, there is rather diffuse subdural hemorrhage smeared over the inner surface of the dura at the base in the anterior, middle and cerebral portions of the posterior fossa.

In addition, there is some isolated diffuse subarachnoid pial hemorrhage over the superior surface of the left frontal lobe and also an area of hemorrhage into the meninges, but distinct hemorrhage into the cortex with the reaction in the underlying white matter, which now has edematous gelatinous and slightly yellowish tinge. Elsewhere, the brain shows no lesions except for pallor. The base of the skull is normal. The pituitary is grossly normal. No toxicologic tests were done since, by the time the patient died, the drug had been eliminated from the system.

Anatomical diagnosis: Aplastic anemia with atrophic pale bone marrow. Hemorrhagic diathesis with subdural and cerebral cortical hemorrhage. Hemorrhages in the temporal muscles. Interstitial hemorrhage in the stomach with mucosal hemorrhage and bleeding into the stomach. Interstitial and subpleural hemorrhages in lungs. Subepicardial, interstitial and subendocardial hemorrhages of the heart. Severe hemorrhage into the renal pelves with extension into the urinary bladder. Hemorrhage into the bladder mucosa and with blood cast in the lumen of the urinary bladder. Interstitial medullary hemorrhage of both kidneys, with pallor of the organs. Diffuse purpuric eruption of the skin. Bilateral periorbital ecchymosis. Subconjunctival hemorrhages. Gingival hemorrhages.

Cause of death: Aplastic anemia with hemorrhagic diathesis and intracranial and visceral hemorrhage.

History of therapeutic administration of Chloromycetin during the Spring of 1960 for the treatment of measles and other infections.

It is admitted that Chloromycetin, despite its hazards, is a valuable drug and perhaps the drug of choice in Salmonella infections and in severe Hemophilus-influenza meningitis, typhoid, croup and pneumonia. While its value justifies its use in well selected conditions, it should not be used, however, when other antibiotics such as penicillin and the Tetracyclines are equally effective. Whenever Chloromycetin therapy is used, regular and frequent blood studies should be done and at the first manifestation of a hemotoxic effect, the drug should immediately be discontinued. It is also recommended that when Chloromycetin is used, the oral administration is preferable to the parenteral. The parenteral administration should only be used when a patient is totally unable to take it by mouth or where oral ingestion results in diarrhea or gastroenteritis. It has been demonstrated that intramuscular administration does not give any higher blood levels nor does it produce more rapid absorption.

Chloromycetin is a broad spectrum antibiotic with a wide range of activity against certain serious bacterial gram positive and gram negative organisms, rickettsial infections, and against many resistant staphylococci. The oral dose varies with the condition. The recommended dose for adults is 25-50 mg per kg of body weight per day in divided doses for several days or until symptoms are controlled. The interval between doses is 4-6 hours. The dose for children is 50-100 mg per kg of body weight per day in divided doses (6 hour intervals) until control is established. The dose should then be reduced to 30-50 mg per kg daily.

It is emphasized that the drug should always be used with the utmost caution, under strict medical supervision where it is distinctly the drug of choice in serious infections. It requires frequent blood studies because of the numerous blood dyscrasias associated with its use. The following blood disorders have been associated with the use of Chloromycetin, thrombocytopenic purpura, granulocytopenia, purpura, pancytopenia and aplastic anemia.

Although warning labeling against the use of Chloramphenicol in minor infections and the need for adequate blood studies during its administration had been recommended by a committee of the Na-

tional Research Council and have been in effect since 1952, the Medical Director of the Food and Drug Administration indicated that in some cases the drug has been used in minor conditions in total disregard of labeling warning statements. Also, it has been employed not uncommonly in conditions for which safer and equally effective drugs were valuable and actually where the use of antibiotics was not indicated. A re-evaluation was therefore considered necessary. This indiscriminate use of the drug again raised the question as to whether it should be taken off the market entirely or should be restricted for use in hospitalized patients, or continue in use, but under revised patterns of labeling which would be more widely and more readily available to physicians.

Because of the greater frequency of reported blood dyscrasias associated with the increased use of the drug, a panel of distinguished physicians was appointed by the National Research Council at the request of the United States Food and Drug Administration in order to carry out this re-evaluation. Commissioner George B. Larrick of the Food and Drug Administration recently announced that the panel recommended precautions in the use of this drug. They found that Chloramphenicol is a valuable drug which should not be removed from the market despite its potential hazards, but should remain in use, under medical supervision, in the treatment of serious infections. They also recommended that the package containing the drug should carry a warning against its possible use in minor infections and a statement urging physicians to do adequate and frequent blood studies when the drug is being used.

The National Research Council panel recommended that: "The information should be disseminated as a warning on the drug label and elaborated in an enclosure in the drug package. Beyond this, there is need for the continuing education of the physician through the media of medical meetings and medical literature. This, of course, is a responsibility of the leaders of medicine and not of the Food and Drug Administration."

On the role of individual and specific responsibility, the panel recommended: "More effective education of physicians in the proper use of drugs must be a continuing consideration. The role of pharmaceutical companies in postgraduate medical education cannot be overestimated. Leaders in medicine must face this situation boldly and realistically if standards of practice are to be improved. The medical educators who constitute the editorial boards

of a number of medical journals could exert some influence if they would improve the advertising that appears in their journals."

Dr. William Kessenich, the Medical Director of the Food and Drug Administration, recently stated that regulations covering labeling of Chloromycetin are now being revised and these will require an insert in every package of the drug for all parenteral use. The insert will call attention to the hazards associated with the use of the drug, the indications for its proper use, and the need for repeated blood studies during its use.

It is gratifying to relate that the manufacturer of Chloromycetin is already cooperating with the Food and Drug Administration and is relabeling the drug in compliance with the Committee's recommendations.

It must be pointed out that while the drug is life-saving in certain severe infections, such as typhoid and other drug-resistant staphylococcus infections, it is a hazardous drug which may produce serious blood disorders, some of which can be fatal as in the case cited above.

Physicians have a special responsibility in using any drug with a high known incidence of side and untoward reactions. This high incidence means the assumption of a calculated risk, requiring in each use so much special attention that is should discourage casual use. We again take this opportunity to request physicians to report all side reactions resulting from the use of any drug, either from accidental ingestion or from iatrogenic causes.

In addition to iatrogenic accidents, accidental ingestions of the drug by children are also being reported. This drug originally prescribed for adults is carelessly handled and easily accessible to unsuspecting children who ingest it and may develop serious consequences. Along with the revised labeling precautions, the physician should also warn patients when prescribing this drug about its potential hazards, the need for proper storage and handling, and the importance of keeping it at all times securely away from the reach of children.

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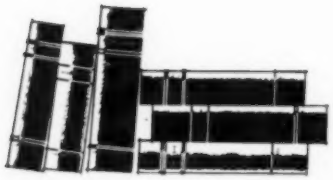
(This is the sixth of a series of papers by Dr. Jacobziner)



. . . Books

Edited by

MICHAEL A. BRESCIA, M.D.

BLOOD DISEASES OF INFANCY AND CHILDHOOD. Carl H. Smith. St. Louis, C. V. Mosby Co. 1960. 572 pp. $17.

Although the hematological states met in infancy and childhood correspond in the great majority of instances to those which we find in the adult, it is the pediatrician who first comes in contact with a very large group of disorders of the blood directly evolved through genetic transmission. For as long as pediatrics and adult medicine are practiced independently, there will be a need for a book, such as this one written by Dr. Smith. He is a pediatrician in active practice who has had a known interest bound to clinical research in hematology. His book is comprehensive, covering all phases of hematology, yet concise and informative. It is documented by bibliographical data, supplemented by the author's bedside experience. LUIS A. AMILL, M.D.

CARE OF THE WELL BABY. By Kenneth S. Shepard, M.D. and other contributors. Paper. Pp. 224. Illustrated. J. B. Lippincott Co. Philadelphia 1960. $3.25.

The author has confined the subject matter of this small volume to the management of the child from birth to two years of age. This is a period of uncertainty and anxiety to the new mother and so the author directs his attention to the importance of the doctor-parent relationship and the proper approach. The book is not intended as a profound pediatric text-book but rather a primer for the neophyte.

The author discusses succinctly and sensibly many of the vexing problems of the first year such as sleep requirements, finger-sucking, toilet training, the umbilicus etc. He is forthright and to the point particularly in discussing the treatment of colic in which the injunction is: "send grandmother on a distant vacation!" The feeling many times might be to send grandmother to the nether land as well but this might be impractical if one were to maintain peace within the family constellation.

The book has many practical aspects and is recommended to all who are to begin the care of infants outside of the sheltered atmosphere of the hospital.—M.A.B.

The Cover . . .

Archives of Pediatrics is pleased to join in the 150th Anniversary salute to The Massachusetts General Hospital, Boston, by presenting a striking aerial view of this famous institution. Chartered in 1811, its original hospital building—Bulfinch—was open to patients in 1821 and has been in continuous use ever since. The pediatric department—Burnham Memorial—shares a building with the Vincent Memorial for women.

Coincidental with the MGH Anniversary program, announcement has been made of the more than a million dollar gift from the Joseph P. Kennedy, Jr. Memorial Foundation for the establishment of Laboratories for Research on Mental Retardation in children. In process of construction, the Memorial Laboratories will be directed by a group of outstanding Massachusetts General and Harvard Medical specialists and professors. Something of the remarkable progress which has so far been achieved in this important research unit will be included in the May issue of Archives.

General Information . . .

Archives of Pediatrics is published every month to provide an independent journal through which pediatric specialists and others who have data of importance in this field, can present their original material and research findings.

Contributions invited from practicing physicians and clinicians whose ancillary services include such specialties as pathology, radiology, odontology, psychology, etc. Please submit only manuscripts not previously published; send typewritten original and copy, double-spaced—attention Editor. (Views and statements are sole responsibility of the author.)

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on the pathogenesis of pyelonephritis:

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."[1]

The "exquisite sensitivity"[2] of the medulla to infection (as compared with the cortex), highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."[3]

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References: 1. Schreiner, G. E.: A.M.A. Arch. Int. M. **102**:32, 1958. 2. Freedman, L. R., and Beeson P. B.: Yale J. Biol. & Med. **30**:406, 1958. 3. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958.

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FOR DIAGNOSIS: If cow's milk allergy is suspected, a 24- to 48-hour trial period with Sobee often eliminates the need for an allergy study.

1. Clein, N. W.: Pediat. Clin. North America, Nov., 1954, pp. 949-957.

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